Reducing the Cardiovascular Consequences of Diabetes Mellitus

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Type 2 diabetes is an important, independent risk factor for cardiovascular disease. As a result of the pandemic explosion of Type 2 diabetes, reducing the human and financial consequences of the disease is a major healthcare concern. In primary prevention, antihypertensive treatment, aspirin and lipid-lowering intervention are effective at reducing the incidence of coronary heart disease although the beneficial effect of optimal glycaemic control remains to be conclusively proven. Type 2 diabetic patients with acute myocardial infarction should receive a specific programme of intensive treatment, which includes optimal glycaemic control using intensive insulin treatment, thrombolysis, and early use of beta-blockers and angiotensin-converting enzyme inhibitors. Secondary prevention is also essential because beta-blockers and lipid interventions are more effective in Type 2 diabetic patients than in non-diabetic patients with coronary artery disease. Unfortunately, too many Type 2 diabetic patients do not receive adequate treatment or do not comply with their long-term medical recommendations. © **1998 John Wiley & Sons, Ltd.**

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Introduction

Type 2 diabetes is a major independent risk factor for cardiovascular disease.[1] Although epidemiological research in diabetes and cardiovascular disease has been made difficult by inconsistent definitions and methods of detection, many studies have found increased rates of coronary heart disease (CHD) in diabetic patients compared with non-diabetic people. The relative risk of death from CHD in Type 2 diabetic patients compared with matched non-diabetic people ranges from 1.5–2.5 in men and 1.7–4.0 times in women, with the relative risk being consistently higher in women than in men. At least 50 % of all deaths in Type 2 diabetes are caused by CHD, and cerebrovascular disease accounts for another 15 %. Peripheral vascular disease is also a frequent and severe complication; Type 2 diabetic patients have a 10- to 15-fold higher risk for lower extremity amputations compared with non-diabetic people. The United Kingdom Prospective Diabetes Study (UKPDS) Group followed 4209 newly diagnosed Type 2 diabetic patients for 20 years and found that 31 % were affected by major cardiovascular events, mainly CHD, at the end of this period. Reducing the human and financial cardiovascular consequences of Type 2 diabetes is currently a major healthcare concern because of the pandemic increase in the incidence of the disease. This review will focus on CHD, the leading cause of premature death in the Type 2 diabetic population.

Although the line between primary and secondary cardiovascular prevention is thin, especially in Type 2 diabetic patients, the primary prevention of CHD, treatment of myocardial infarction (MI) and secondary cardiovascular prevention are all discussed. Currently, we have effective treatments to reduce cardiovascular morbidity and mortality significantly in Type 2 diabetic patients. However, these drugs are often ill-used by patients and physicians.

Primary Prevention

Reducing the incidence of coronary events in Type 2 diabetic patients who have no clinical evidence of CHD may be accomplished through the following:

Effect of Optimum Glycaemic Control

In Type 2 diabetic patients, poor glycaemic control is associated with an increase in the frequency of micro- and macrovascular complications.[2] However, the non-significant reduction in macrovascular events in young Type 1 diabetic patients enrolled in the Diabetic Control and Complications Trial (DCCT) cannot be extrapolated to older Type 2 diabetic patients because up to 40 % of Type 2 diabetic patients already have cardiovascular diseases at diagnosis. The University Group Diabetes Program (UGDP) data did not support a beneficial effect of improved glycaemic control on the incidence of

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cardiovascular events in Type 2 diabetic patients.[3] In the UKPDS, intensive blood glucose control, by either oral agents or insulin, significantly decreased the risk of microvascular complications. There was evidence, albeit inconclusive, of a 16 % risk reduction ($p = 0.052$) for myocardial infarction, which included non-fatal and fatal myocardial infarction and sudden death. None of the individual drugs had an adverse effect on cardiovascular complications;[4] however, it must be emphasized that the combination of diet, exercise and the use of oral hypoglycaemic agents or insulin, results in poor long-term glycaemic control in many Type 2 diabetic patients.

Effect of Antihypertensive Treatment

The prevalence of arterial hypertension in Type 2 diabetic patients is higher than in the general population. The relationship of arterial blood pressure to CHD has been reported to be similar in diabetic and non-diabetic people.[4] In intervention studies, the reduction of blood pressure has decreased the incidence of CHD in diabetic patients although by less than would have been expected.[5] In the subset of patients with hypertension in the UKPDS, blood pressure control was more effective than blood glucose control in reducing the risk of macrovascular complications. A mean decrease of 10 mmHg for systolic pressure and 5 mmHg for diastolic pressure was associated with significant reductions in deaths related to diabetes and in strokes. Atenolol and captopril used as first-line therapy were equally effective and safe in lowering blood pressure and reducing the risk of fatal and non-fatal macrovascular complications. After nine years of follow up, 29 % of patients allocated to tight blood pressure control required three or more antihypertensive drugs to achieve target blood pressure values, making the evaluation of single drugs very difficult.[6] Long-term poor compliance with treatment is a major problem in asymptomatic hypertensive Type 2 diabetic patients, and the education of the patient and his or her family is mandatory and an important component of treatment.

Effect of Lipid Intervention

In Type 2 diabetic patients, the most frequent dyslipidaemia is hypertriglyceridaemia and a decrease in high-density lipoprotein (HDL) cholesterol. Several studies indicate that these abnormalities are associated with a higher incidence of CHD in Type 2 diabetic patients.[7] With persistent dyslipidaemia, despite dietary lipid restriction and improved glycaemic control, hypolipidaemic agents should be used. However, evidence is scarce on the cholesterol-lowering effect of different interventions on the risk of CHD in diabetic patients. The Helsinki Heart Study, using gemfibrozil, included 135 Type 2 diabetic patients. The 5-year incidence of major CHD events in diabetic patients was 3.4 % in the gemfibrozil-treated group and 10.5 % in the placebo-treated group ($p = 0.19$).[8] In the West of Scotland Coronary Prevention Study (WOSCOPS), a beneficial effect of pravastatin (40 mg once daily) was shown in primary prevention in patients with total cholesterol >6.5 mmol·l^{-1} but no information is available on the diabetic patients included in this study.

Aspirin

Coagulation factors as well as platelet adhesion and aggregation are abnormal in diabetes. The meta-analysis of randomized trials of antiplatelet therapy by the Antiplatelet Trialists' Collaboration found a benefit of aspirin treatment in Type 1 and Type 2 diabetic patients with, or at an increased risk of, vascular disease.[8] The combined end-point of vascular death, MI and stroke was 22.3 % in the control group and 18.5 % in people receiving aspirin. The benefit of aspirin therapy was similar in diabetic and non-diabetic people.[8] In the Early Treatment Diabetic Retinopathy Study, 3711 diabetic patients were enrolled and followed up for 7 years.[9] The reduction in cardiac events with aspirin was similar to that observed in other trials.[9] These two studies investigated primary and secondary cardiovascular prevention. Treatment with a low dose of aspirin should be considered for all Type 2 diabetic patients with CHD or at high risk of CHD.[10]

Non-pharmacological Interventions

The cessation of smoking and increased physical activity have beneficial effects on glycaemic control, hypertension, dyslipidaemia and insulin resistance. These inexpensive, non-pharmacological interventions may have a beneficial effect on CHD primary prevention in Type 2 diabetic patients although no randomized trial has tested this hypothesis in Type 2 diabetic patients.

Acute Myocardial Infarction

Sudden death and acute MI are often the first manifestations of CHD in Type 2 diabetic patients. Patients with Type 2 diabetes are at an increased risk of MI compared with the general population. In-hospital and one-year mortality after MI are twice as high as for non-diabetic individuals. Women with diabetes have a poorer prognosis after MI than men with diabetes. These data have been reported repeatedly during the past 20 years, and the increased mortality in diabetic patients compared with non-diabetic people was not reduced during the past two decades.[11]

Glycaemic Control

Optimum blood glucose control in Type 2 diabetic patients with an acute MI was effective in the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction study (DIGAMI). Six hundred and twenty

diabetic patients, most with Type 2 diabetes, were randomly allocated to intensified treatment with a combined insulin and glucose infusion for at least 24 hours, followed by subcutaneous insulin for at least 3 months, or usual care via diet and oral antidiabetic agents. Intensive insulin treatment was associated with a significant reduction (30 %) in mortality at 1 year,[12] and the survival benefit was maintained for 5 years.[13] The fact that the greatest benefit was observed in those patients not treated previously with insulin raises the possibility that withdrawal of oral hypoglycaemic agents may also have contributed. Metformin must be discontinued in Type 2 diabetic patients with acute MI because of increased risk of lactic acidosis.

Thrombolysis

In the Second International Study of Infarction Survival (ISIS-2) study, the mortality in diabetic patients was 17.2 % in the placebo-treated group and 11.8 % in the streptokinase-treated group. This 38 % reduction in mortality in diabetic patients was higher than the reduction observed in non-diabetic individuals (22 %).[14] The review by the Fibrinolytic Therapy Trialists' Collaborative Group confirmed the benefit of thrombolysis in diabetic patients; the absolute reduction in mortality was higher than that seen in non-diabetic patients.[15] No data are currently available on the comparison of angioplasty with thrombolysis in Type 2 diabetic patients with acute MI.

Beta-blockers

Beta-blockers have been avoided often in diabetic patients treated with insulin because of the concern of severe prolonged hypoglycaemia; this is not an issue with the use of cardioselective beta-blockers. Two studies were carried out to investigate the effect of metoprolol administered soon after MI in 413 and 120 diabetic patients with acute MI. In the first study, mortality reduction at 15 days was 49 % and in the second study, mortality at 3 months was reduced by 58 %. The beneficial effect of metoprolol in diabetic patients was greater than that obtained in non-diabetic patients.[16]

ACE Inhibitors

In patients with acute MI and heart failure or left ventricular dysfunction, different studies have shown that various ACE inhibitors reduce cardiovascular mortality. In the GISSI-3 study, lisinopril 5–10 mg once daily during the first 24 hours in Type 2 diabetic patients with acute MI reduced the 6-week mortality to 7.7 % compared with 10.5 % in the patients on placebo.[17] Lisinopril and probably all the other ACE inhibitors should be used as soon as possible in all Type 2 diabetic patients with acute MI.

Type 2 diabetic patients with acute MI should have specific care. The management of these patients should include: optimum glycaemic control using insulin with rigorous prevention of severe hypoglycaemia; thrombolysis if indicated; aspirin; early beta-blockade; and ACE inhibition. Unfortunately, too many Type 2 diabetic patients do not receive such management during the acute phase of MI at present.

Secondary Prevention

In Type 2 diabetic patients with chronic coronary artery disease or with previous MI, different studies have shown that the 5-year mortality and the incidence of re-infarction are higher in diabetic patients than in non-diabetic people. In Type 2 diabetic patients, secondary cardiovascular intervention is important and may be more effective than in non-diabetic individuals. Unfortunately, this type of intervention is commonly poorly performed.[18]

Aspirin

Aspirin use is associated with a reduction of cardiovascular morbidity and mortality in diabetic patients with various types of cardiovascular atherosclerotic disease.

Beta-blockers

Cardioselective beta-blockers are also effective when administered long-term after MI. In randomized, controlled trials of beta-blocker treatment, patients with diabetes had a 48 % reduction in mortality, compared with a 33 % reduction in the general population.[19] A study of atenolol in patients with or at risk of CHD who had non-cardiac surgery provides further evidence of benefit in diabetic patients. Diabetes was the strongest predictor of death. Compared with non-diabetic patients, diabetic patients on atenolol had no increased risk of death, whereas those given placebo had a four-fold increase in risk.[20]

Lipid Intervention

The Scandinavian Simvastatin Survival Study was designed to assess the effect of cholesterol reduction with simvastatin on mortality and morbidity of patients with CHD. A total of 4444 patients with previous angina or MI, and with serum cholesterol levels of 5.5–8.0 $mmol \cdot l^{-1}$ and serum triglyceride levels below 2.5 $mmol \cdot l^{-1}$ were randomly selected to receive simvastatin or placebo. Over the 5.4-year, median follow-up period, simvastatin significantly reduced CHD mortality by 42 % and all-cause mortality by 30 %. The incidence of major CHD events was reduced by 34 %.[19] A subgroup analysis of diabetic patients included in the trial showed that the benefit was even greater in diabetic patients compared with non-diabetic patients.[20] Similar data were observed in the subgroup of normocholesterolaemic diabetic

patients with CHD included in the Cholesterol and Current Events study (CARE).[21]

The cessation of smoking and the prescription of a cardioselective beta-blocker, aspirin and a statin are effective in secondary cardiovascular prevention interventions. These treatment strategies reduce cardiovascular morbidity and mortality but in routine practice too many Type 2 diabetic patients as well as non-diabetic patients with CHD do not receive such treatment.

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